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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/765,837	09/07/99	LAUB R	VANMA48.001A

HM22/0213

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EXAMINER	
CLEMENS,K	
ART UNIT	**PAPER NUMBER**
1644	13

DATE MAILED: 02/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/765,837	LAUB ET AL.	
	Examiner	Art Unit	
	Karen Clemens	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 1997 and 27 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-36 and 39-42* is/are pending in the application.

4a) Of the above claim(s) *40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-36 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. This application is a national stage filing under U.S.C. 371 from PCT/BE95/00063, filed 7/14/95. Applicant should amend the first line of the specification to include the relationship to this priority document.

2. Claims 31-36 and 39-42 are pending.

3. Applicant's election without traverse of Group I, claims 31-36 and 39 in Paper No. 9, dated 11/27/00 is acknowledged. Claims 40-42 are being withdrawn from further consideration by the Examiner as being drawn to nonelected inventions (see 37 C.F.R. 1.142(b)).

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

5. Claims 31-36 and 39 are presently under examination.

6. Drawings have been submitted which fail to comply with 37 C.F.R.1.84. Please see the enclosed form PTO-948.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 31-36 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to

this rejection are the scope of the claim, the amount of direction or guidance provided, the unpredictability in the art and amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The specification discloses a series of Factor VIII peptides which are predicted to constitute antigenic polypeptides and conformational epitopes based on hydrophilicity, flexibility and accessibility determinations for various regions within the C-terminal region of Factor VIII. The antigenic polypeptides and epitopes are essential in identifying Factor VIII inhibitors, usually antibodies, often found in Hemophilia A patients and which can interfere with Factor VIII function (see specification page 4, lines 19-30, page 8, lines 9-23, page 10, lines 2-16 and page 17, lines 25-35 in particular).

Although Applicant has designated a series of peptide fragments for use in testing patient sera for Factor VIII inhibitor antibodies, and has generated antibodies to the peptides of SEQ ID NO:2 (Asp 1681-Arg 1696) and SEQ ID NO:13 (Asp 327-Met 355), it is unclear if these peptides constitute antigentic regions and epitopes which represent those found on the intact Factor VIII molecule. Moreover, it is unclear if these peptides constitute antigenic regions and eptiopes accessible on the Factor VIII molecules in patient sera and if the Factor VIII-specific inhibitor antibodies in these patients will recognize these isolated peptides in diagnostic assays and further whether these peptides can be used in a pharmaceutical composition for therapeutic purposes.

The current state of the art in epitope structure prediction is limited given that noncontiguous amino acid residues constitute most epitopes, and that the dynamics of binding is often not integrated into the epitope prediction equation, making epitope structure prediction a complex four-dimensional problem (see Van Regenmortel, page 465, abstract in particular; *Methods: A Companion to Methods of Enzymology* 9:465-472). Van Regenmortel notes that 90% of antibodies raised against intact proteins do not react with any peptide fragment derived from the parent protein indicating that these antibodies are directed to discontinuous epitopes (see page 466, column 1 in particular). In addition Van Regenmortel states that the low success rate of antigenic prediction is due to the fact that predictions concern only continuous epitopes and it is unrealistic to reduce the complexity of epitopes that always possess conformational features to one-dimensional, linear peptide models (see page 467, column 2 in particular).

Furthermore, Palmer et al. (*Vox Sanguinis* 72:148-161) using synthetic peptide arrays to identify novel factor VIII inhibitor epitopes note that each patient's pattern of anti-Factor VIII antibody reactivity appeared to be polyclonal, directed against multiple sites located within the amino and carboxyl terminus of the protein, and was unique for each plasma investigated (see page 156, column 1 in particular). In addition Palmer et al. further note that in this assay most inhibitor plasma showed weaker reactivity to a number of other synthetic peptides in the amino and carboxyl terminal and other domains suggesting that the peptides may only represent a portion of the complete (linear or discontinuous) epitope. In some cases Palmer et al. found that significantly reactive eptiopes could not be identified using this assay, suggesting that the Factor VIII epitope(s) normally recognized by these antibodies is/are incompletely represented on the peptide arrays. Moreover, Palmer et al. note that it is difficult to predict the importance that any given antibody:epitope interaction may have on Factor VIII procoagulant activity based on the results of synthetic peptide assays alone (Pin screening) due to our incomplete understanding of the relationship between structure and function of the different FVIII domains and the possibility that both inhibitory and noninhibitory antibodies may be present in the patient's plasma (see page 157, column 2 in particular). Palmer et al. adds that the patient-specific pattern of reactivity against multiple peptides and the limitation of detecting linear epitopes but not discontinuous epitopes are further complications.

Therefore, to use the instant invention as intended the skilled artisan would require additional guidance in regard to which amino acids contribute antigenic polypeptides and functional Factor VIII epitopes, which epitopes are recognized by patient sera, which antibodies in patient sera that recognize those epitopes inhibit Factor VIII function, and whether administration of the peptides could by used to block function of the inhibitor Factor VIII antibody. Therefore for the skilled artisan to practice the invention as broadly claimed would require experimentation that is excessive and undue.

In view of the quantity of experimentation necessary, the unpredictability in the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention."

Claims 31, 33, 34, 35, 36 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A. Claims 31, 33, 34, 35, 36 and 39 are indefinite and ambiguous in the recitation of the polypeptide sequence "contained between arginine 1652 and arginine 1696 inclusive,....contained between threonine 1739 and aspartic acid 1831 inclusive, ...contained between glutamic acid 1885 and arginine 1917 inclusive." The polypeptide sequence of A3 of Factor VIII is not found in the specification as filed. Therefore, it is not clear as to the exact identify of amino acid residues 1652-1696, 1739-1831 and 1885-1917 recited in the claims. As is evidenced by the specification on page 2 (lines 1-7 in particular) the complete structure of the *plasma* FVIII in unknown as is the precise structure of the carbohydrates.

B. It is improper to recite "epitopes of Claim 32" in Claim 34, and the "fragment of Claim 31" in Claims 36 and 39 because an "antigenic polypeptide" is recited in base Claims 31 and 32.

C. The word "An" should be inserted in Claim 33, line 1, before "antigenic".

D. Claim 33 is unclear in the recitation of "at least either tyrosine or histidine linked". It is unclear to which residue tyrosine or histidine would be linked.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> "A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims 31-33, 36 and 39 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,965,199.

The '199 Patent teach the antigenic polypeptides of at least 7 amino acids of the polypeptide sequence A3 of factor VIII having an amino acid sequence contained between amino acid residues 1652-1696, 1739-1831 and 1885-1917 of Factor VIII (see Figure 10 in particular). The '199 Patent further teach fusion or carrier proteins of the Factor VIII peptides which are linked to the Factor VIII peptide and which could include either tyrosine or histidine "linked" to the peptide (see column 39, lines 48-53 and column 40, lines

31-34 in particular). The '199 Patent further teach a pharmaceutical composition comprising a peptide of Factor VIII and an acceptable pharmaceutical vehicle (see column 40, lines 56-61 in particular).

Therefore, the reference teachings thus anticipate the claimed invention.

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Clemens whose telephone number is (703) 308-8365. The examiner can normally be reached Monday through Friday from 8:00 AM to 5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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February 9, 2001

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